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10/588,597	02/04/2007	Akio Matsuhisa	5426FP-1	9532

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EXAMINER	
BABIC, CHRISTOPHER M	
ART UNIT	PAPER NUMBER
1637	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/588,597	MATSUHISA ET AL.	
	Examiner	Art Unit	
	CHRISTOPHER M. BABIC	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,5-10 and 19-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,5-10 and 19-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/9/09; 11/16/09; 8/28/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claim(s) 3, 5-10, and 19-31 are pending and under examination. The following Office Action is in response to Applicant's communication dated March 1, 2010.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on November 9, November 16, and December 2009 were filed after the mailing date of the NON-FINAL Office Action on August 28, 2009. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 112 - Indefiniteness - Withdrawn

Applicant's claim amendments and/or supplemental remarks are sufficient to overcome the rejection of claim(s) 1, 3, 5-10, 19, and 20 presented in the Office Action dated August 28, 2009. Thus, the rejection has been withdrawn.

Claim Rejections - 35 USC § 102 - Withdrawn

Claim 1 has been canceled rendering the previous rejection over Hu moot.

Claim Rejections - 35 USC § 103 - Maintained

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 3, 9, 10, 19, 21-23, and 28-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nuovo et al. (Genome Res. 1993 2: 305-312) in view of Hu (U.S. 5,939,251).

The claimed invention requires that amplified nucleic acid exist in the PCR solution outside of the cell (see "determining" and "detecting" step). With regard to the newly amended claim requiring "dry fixation" (teaches fixation in 95% ethanol), "pre-treating", and "performing" steps, Nuovo teaches performing in situ PCR (pg. 305-306,

materials and methods, for example). With regard to detection of amplified nucleic acids existing outside of cells, the reference expressly teaches,

"... the amplifying solution was retrieved, its DNA separated on an agarose gel, and DNA sequences homologous to the internal fragment of the bcl-2 gene were analyzed using a 32p-labeled probe and Southern hybridization (pg. 307; see also fig. 1A),..., the present study showed that amplification occurred in ethanol- and acetone-fixed cells, but PCR product was primarily detectable in the amplifying solution (pg. 309)."

Nuovo does not expressly teach divided compartments of a support.

The teachings of Hu have been outlined previously in the NON-FINAL Office action dated August 28, 2009 (see pg. 3-4). The reference further highlights,

"The techniques as disclosed can flexibly define a sealed space for carrying out certain molecular biological reactions therein such that wastes of expensive reagents required for the reactions can be reduced because the sealed space can be more conveniently reconfigured depending on the volume of the reaction samples and the space necessary for carrying out each reaction. Furthermore, the enclosure materials can be conveniently and safely removed after completion of the reactions such that the main purposes of the reactions can be achieved without being limited by difficulties caused by post-reaction processes. Because that a secure and flexible sealed configuration is created, large number of the same type of sealed spaces can be conveniently and simultaneously provided and the amplification and detection processes during and after the reactions can be flexibly carried out without being limited by the concerns that leakage or breaks of the sealed spaces may occur in conducting the detection or reaction processes (col. 8)."

Thus, in summary, it is submitted that it would have been *prima facie* obvious to a person of ordinary skill in the art at the time of invention to utilize the products and methods of Hu to perform the in situ PCRs methods of Nuovo since Hu expressly recognizes that the such PCRs could be performed more efficiently within such products.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive.

The phrase "dry fixation" is not defined within the claim or specification to distinguish the claimed invention from the fixation teachings from Nuovo. The closest definition of the phrase "dry fixation" found by the examiner is found on page 17 of the specification, which recites, "...a dehydration method in which the protein is quickly denatured and immobilized on a carrier." As pointed out by Applicant (see remarks middle pg. 8), Nuovo clearly teaches fixation of cells with ethanol and acetone (pg. 306, col. 1); as understood by the examiner, two components commonly used in dry fixation techniques. In any event, such fixation necessarily dehydrates the cells, as well as denatures and immobilizes the protein of cells through ethanol or acetone. Furthermore, whether the slide itself was bathed in ethanol or acetone then removed, or an appropriate aliquot of ethanol or acetone was placed on the slide for fixation of cells, the fixation methods in Nuovo clearly posses a degree of drying as ethanol and acetone evaporate in air to a much larger degree than formalin.

Applicant points to examples 1 and 2 of the specification for support of the phrase "dry fixation," however Applicant is reminded that although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). As understood by the examiner, the inventive concept of the claimed invention is the fixation of cells such that the cellular wall allows for passage of nucleic acid to a level past that commonly accepted for in situ PCR, i.e. drying fixed cells out to a point where

large amounts of nucleic acid leak from them . Such a concept, i.e. promoting leakage of nucleic acid from fixed cells for amplification purposes, has not been found in the prior art. Thus, an amendment reciting the specifics of the fixation method that promotes nucleic acid leakage, such as those conditions in examples 1 and 2, would obviate the instant rejection.

Thus, the rejection is maintained.

Claim Rejections - 35 USC § 103 - New Grounds

The following rejection(s) is/are made in view of Applicant's amendments.

1. Claims 5, 20, 24 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nuovo et al. (Genome Res. 1993 2: 305-312) in view of Hu (U.S. 5,939,251) as applied to claims 21 and 22 above, and in further view of Villeponteau et al. (U.S. 5,776,679).

The teachings of the previously applied reference(s) have been outlined in the above rejections. The previously applied reference(s) do not expressly teach the labeling of nucleic acids during PCR or detection of PCR products through electrophoresis.

Villeponteau provides a supportive disclosure that teaches labeling nucleic acids during in situ PCR through the incorporation labeled nucleotides (col. 42, lines 50-65,

for example). The reference highlights that labeled nucleotides prevent leakage of PCR products.

Thus, in summary, it is submitted that it would have been *prima facie* obvious to a skilled artisan at the time of invention to incorporate labeled nucleotides into in situ the PCR of Hu since the prior art expressly suggests such a modification to prevent leakage of PCR products.

With regard to the detection of PCR products through electrophoresis, such a concept was well known as a standard method of PCR product detection. Villeponteau teaches such an electrophoresis method (col. 31, example 3, for example).

Thus, in summary, it is submitted that it would have been *prima facie* obvious to a person of ordinary skill in the art at the time of invention to detect the PCR products of Hu by electrophoresis since the prior art recognized such a modification as standard within the art.

2. Claims 6-8 and 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nuovo et al. (Genome Res. 1993 2: 305-312) in view of Hu (U.S. 5,939,251), in view of Villepontueau et al. (U.S. 5,776,679) as applied to claims 5 and 24 above, and in further view of Stapleton et al (US 6,103,192).

The previously applied reference(s) do not expressly teach the detection of labeled PCR products through hybridization to immobilized probes in microarray format.

Stapleton provides a supportive disclosure that teaches a method wherein various biological specimens are collected, dried, transported, stored and processed on matrixes which adhere cells and viruses. The method involves fixing such samples to the matrixes, exposing the samples by heating them (col.17, lines 31-32, for example), applying the matrixes to thin-walled tubes for amplification (col. 17, lines 23-35; col.22, example 22, for example), and detection by either gel electrophoresis (col.17, lines 10-15; col.22, example 22, for example), or by applying the amplified product and detector probes to a probe array comprising capture oligonucleotides (col.16, lines 9-60; col.24, lines 21-50, example 7, for example). Furthermore, Stapleton states that such a detection system eliminates the need for gel electrophoresis, less amplification product is needed as the sensitivity of the detection increases, and allows for multiple oligonucleotide sequences at different array positions to be analyzed in the same detection reaction (col.16, lines 26-28, 57-59).

Thus, in summary, it is submitted that it would have been *prima facie* obvious to a person of ordinary skill in the art at the time of invention to detect the PCR products of Hu through use of immobilized probes in a microarray format since the prior art expressly suggested such a modification to allow for the analysis of multiple sequences at once.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher M. Babic whose telephone number is 814-880-9945. The examiner can normally be reached on Monday-Friday 10:00AM to 6:00PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christopher M. Babic/
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